

A novel mechanism for fast regulation of gene expression

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Yehuda Ben-Shahar, Ph.D., assistant professor of biology, (left) and Xingguo Zheng, a Ph.D. candidate in neuroscience and co-author on the paper, are examining fruit flies in the lab. Credit: Whitney Curtis/WUSTL

Our genome, we are taught, operates by sending instructions for the

manufacture of proteins from DNA in the nucleus of the cell to the protein-synthesizing machinery in the cytoplasm. These instructions are conveyed by a type of molecule called messenger RNA (mRNA).

Francis Crick , co-discoverer of the structure of the DNA molecule, called the one-way flow of information from DNA to mRNA to protein the "central dogma of molecular biology."

Yehuda Ben-Shahar and his team at Washington University in St. Louis have discovered that some mRNAs have a side job unrelated to making the protein they encode. They act as regulatory molecules as well, preventing other genes from making protein by marking their mRNA molecules for destruction.

"Our findings show that mRNAs, which are typically thought to act solely as the template for protein translation, can also serve as regulatory RNAs, independent of their protein-coding capacity," Ben-Shahar said. "They're not just messengers but also actors in their own right." The finding was published in the March 18 issue of the new open-access journal *eLife*.

Although Ben-Shahar's team, which included neuroscience graduate student Xingguo Zheng and collaborators Aaron DiAntonio and his graduate student Vera Valakh, was studying heat stress in fruit flies when they made this discovery, he suspects this regulatory mechanism is more general than that.

Many other mRNAs, including ones important to human health, will be found to be regulating the levels of proteins other than the ones they encode. Understanding mRNA regulation may provide new purchase on health problems that haven't yielded to approaches based on Crick's central dogma.

Is gene expression regulated directly?

Ben-Shahar's original objective was to better understand how organisms maintain their physiological balance when they are buffeted by changes in the environment.

Neuroscientists know that if you warm neurons in culture, he said, the neurons will fire more rapidly. And if the culture is cooled down, the neurons slow down. Neurons in an organism, however, behave differently from those in a dish. Usually the organism is able to cushion its nervous system from heat stress, at least within limits. But nobody knew how they did this.

As a fruit fly scientist, Ben-Shahar was aware that there are mutations in fruit flies that make them bad at buffering [heat stress](#), and this provided a starting point for his research.

One of these genes is actually called seizure, because flies with a broken copy of this gene are particularly sensitive to heat. Raising the temperature even 10 degrees sends them into seizures. "They seize very fast, in seconds," Ben-Shahar said.

"When we looked at seizure (sei) we noticed that there is another gene on the opposite strand of the double-stranded DNA molecule called pickpocket 29 (ppk29)," Ben-Shahar said. This was interesting because seizure codes for a protein "gate" that lets potassium ions out of the neuron and pickpocket 29 codes for a gate that lets sodium ions into the neuron.

Neurons are "excitable" cells, he said, because they tightly control the gradients of potassium and sodium across their cell membranes. Rapid changes in these gradients cause a nerve to "fire," to stop firing, and to repolarize, so that it can fire again.

The scientists soon showed that transcription of these genes is coordinated. When the flies are too hot, they make more transcripts of the *sei* gene and fewer of *ppk29*. And when the flies cooled down, the opposite happened. If the central dogma held in this case, the neurons might be buffering the effects of heat by altering the expression of these genes.

One problem with this idea, though, is that gene transcription is slow and the flies, remember, seize in seconds. Was this mechanism fast enough to keep up with sudden changes in the environment?

Does RNA interference regulate gene expression?

But the scientists had also noticed that the two genes overlapped a bit at their tips. The tips, called the 3' UTRs (untranslated regions), don't code for protein but are transcribed into mRNA.

That got them thinking. When the two genes were transcribed into mRNA, the two ends would complement one another like the hooks and loops of a Velcro fastener. Like the hooks and loops, they would want to stick together, forming a short section of double-stranded mRNA. And double-stranded mRNA, they knew, activates biochemical machinery that degrades any mRNA molecules with the same genetic sequence.

Double-stranded RNA binds to a protein complex called Dicer that cuts it into fragments. Another protein complex, RISC, binds these fragments. One of the RNA strands is eliminated but the other remains bound to the RISC complex. RISC and its attached RNA then becomes a heat-seeking missile that finds and destroys other copies of the same RNA. If the mRNA molecules disappear, their corresponding proteins are never made.

It turned out that heat sensitivity in the fly is all about potassium channel,

said Ben-Shahar. What if, he thought, the two mRNAs stuck together, the mRNA segment encoding the potassium channel was bound to RISC and other copies of the potassium channel mRNA were destroyed. This was another, potentially faster way the neurons might be controlling the excitability of their membranes.

A designer fly provides an answer

Which is it? Is regulation occurring at the gene level or the mRNA level?

To find out, the scientists made designer [fruit flies](#) that had various combinations of the genes and their sticky noncoding ends. One of these transgenic fly lines was missing the part of the gene coding for the ppk29 protein but still made lots of mRNA copies of the sticky bit at the end of ppk29. When there were lots of these isolated sticky bits, sei mRNA levels dropped. This fly was as heat sensitive as a fly completely missing the sei gene.

This combination of genotype and phenotype held the answer to the regulatory problem. First of all, mRNA from one gene (ppk29) is regulating the mRNA of another gene (sei). And, second, the regulatory part of ppk29 is the untranslated bit at the end of the mRNA. When this bit sticks to a complete transcript of the sei gene (including, of course, its sticky bit), the RISC machinery destroys any copies of the sei mRNA it finds.

So the gene that codes for a sodium channel regulates the expression of the potassium channel gene. And it does so after the genes are transcribed into mRNA; it's mRNA-dependent regulation.

The interaction between sei and ppk29 is unlikely to be unique, Ben-Shahar said. The potassium channel is highly conserved among species, and analyses of the genome sequences in flies and in people show that

two of three fly genes for this type of potassium channel and three of eight human [genes](#) for these channels have overlapping 3' UTR ends, just as do *sei* and *ppk29*.

Why does this regulatory mechanism exist? Ben-Shahar hates getting out in front of his data, but he points out that transcribing DNA into mRNA is a slower process than translating mRNA into protein. So it may be, he said, that neurons maintain a pool of mRNAs in readiness, and mRNA interference is a way to quickly knock down that pool to prevent the extra mRNA from being translated into proteins that might get the organism in trouble.

Provided by Washington University in St. Louis

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